REMARKS

By this amendment, claims 2-5, 10, 15, and 16 are revised, new claim 17 is added, and arguments are made to place this application in condition for allowance. Currently, claims 1-5, and 15-17 are before the Examiner for consideration on their merits with claims 6-14 withdrawn from consideration.

The issues raised in the outstanding office action are addressed under the appropriate headings.

Claim Objections

In response to the objections to claims 2-5, these claims have been revised accordingly and the objections should be withdrawn.

35 USC §101

Claims 15 and 16 are rewritten to be in proper method claim format. Thus, the rejection based on 35 USC §101 should be withdrawn.

35 USC §112, second paragraph

In response to the allegations of indefiniteness with respect to claims 3 and 5, each of these claims is revised. Moreover, the preferred embodiment deleted from claim 3 is presented in new claim 17. The rewriting of claims 15 and 16 is also believed to remove any instances of indefiniteness.

As a result of the changes to claims 3, 5, 15, and 16, the rejection based on 35 USC §112, second paragraph, should be withdrawn.

35 USC §112, first paragraph

Claims 1-4, 15 and 16 stand rejected by the Examiner under 35 USC § 112, first paragraph, because the specification would not reasonably provide enablement for all claimed nucleophilic leaving groups. While the Examiner acknowledges enablement for methods involving a charge stabilized nucleophilic leaving group that has a thiol function, a different conclusion is reached for the remaining leaving groups claimed, i.e. for charge stabilized nucleophilic leaving groups having a hydroxyl function.

In this context the Examiner refers to the *Wands* factors for determining whether a disclosure would require undue experimentation. Based on post-published document "Sieber, Angew. Chem. 2004. 43: 493-498", the Examiner alleges that there would be a great amount of unpredictability of the pertinent art since various peptide cyclases would have been found to be inactive with peptidyl SNAC substrates. As a consequence, undue experimentation would be necessary for the skilled person to ensure that all claimed nucleophilic leaving groups would have activated the acyl residue of the linear peptide and that cyclization would have occurred.

Applicants respectfully disagree with the Examiner's conclusion. As an initial remark it is pointed out that the objected claims are all restricted to charge-stabilized leaving groups. These charge-stabilized leaving groups are defined in the description, see page 11, lines 25-33, as follows:

> *Charge-stabilized leaving groups are understood in the present invention to be chemical compounds which possess a thio or hydroxyl group and in which the free electron pair of the thiolate or hydroxylate ion released by the acylation reaction stands in conjugation with other electron pairs from, for example, but not exclusively, C=C or C=N double bonds or in which the thio or hydroxy group is bound to a carbon atom which is, for its part, bound to an aromatic or heteroaromatic ring.*

In other words, the leaving groups covered by the claims either bear a thio group or a hydroxyl group. Further, they have in common that the free electron pair of the thiolate or hydroxylate ion, respectively, stands in conjugation with other electron pairs. Thus, it is not apparent why the positive test results obtained for the charge-stabilized leaving groups bearing a thio group should not apply to charge-stabilized leaving groups bearing a hydroxy group.

It is known to persons skilled in the art that the leaving ability and, therefore, the quality of a leaving group, is dependent upon the ability of the leaving group to stabilize a negative charge, see the specification, page 13, lines 9-12. In the present case, this ability is similar for both groups, i.e., the thio-containing group and the hydroxyl-containing group, at least for two reasons. First, the electron stabilizing capabilities of thiol and hydroxyl functions are comparable as such, cf. page 13, line 12 – page 14, line 3 of the specification. Second and according to the above definition, both the thiol function and the hydroxy function, respectively, stand in conjugation with other electron pairs. In particular, they are bound to an sp^3 C atom, which is directly bound to the aromatic ring (a-C atom). Insofar, the aromatic system has the same inductive effect on each group regardless of whether it is a thio group or a hydroxy group, cf. page 4, lines 14-19 of the specification.

Therefore, it is submitted that the experimental data obtained for thiol-containing leaving groups are not only significant for but indeed transferable to hydroxy-containing leaving groups. This means that, even in the absence of experimental data involving hydroxyl-containing leaving groups, these compounds are sufficiently enabled in light of the working examples provided for the thiol-containing compounds on pages 28-29 and 33 of the specification.

Also, the Examiner's reference to the prior art to support the contention that undue experimentation is required in connection with the invention is also traversed.

First, it is pointed out that the Sieber reference to which the Examiner refers was published in 2004, whereas the priority date of the present application is July 31, 2003. Hence, the objection under 35 USC § 112, first paragraph, is based on a document which was published after the relevant filing date of the application. This is in clear contrast to the principles of the US patent system. As clearly stated in *In re Koller*, it is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 112, first paragraph (*In re Koller*, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 n.5 (CCPA 1980)).

Second, it is emphasized that the Sieber reference relates to tests of peptide cyclases performed on peptidyl SNAC substrates. The claimed leaving groups, however, are fundamentally different from these SNAC substrates, as repeatedly underlined in the present application. In contrast to the established SNAC substrates, thiophenol for example, features, as a charge-stabilized leaving group according to the present invention, no structural analogy at all to the natural cofactor. It provides, however, a

significantly better leaving group quality, as the thiol is in conjugation with an aromatic benzene ring. Within other leaving groups according to the present invention, the thiol function or the hydroxy function is bound to an sp^3 C atom, which is directly bound to the aromatic ring (a-C atom), in such a way that the aromatic system has an inductive effect on the thio groups or the hydroxy groups, see page 4 lines 9-19 of the specification. The expert skilled in the art knows that the inductive effect of an aromatic system has a stabilizing effect on the groups bound to an a-C-Atom, thus, increasing their leaving group quality. In the case of the SNAC, neither a conjugation with an aromatic or heteroaromatic system nor stabilization by the inductive effect of an aromatic system in an a-position to the carbon atom, to which the thio group is bound, is available, thus, many enzymes do not show any activity with these SNAC substrates, see page 4, line 22 – page 5 line 1 of the specification.

Further passages could be cited from which it is clear that SNAC are worse leaving groups than thiophenol from a chemical viewpoint, cf., e.g., page 13, lines 1-8, page 15, lines 16-20 of the specification. As a consequence, in the use of charge-stabilized thiol and hydroxy compounds according to the invention, such enzymes also show cyclization activity which were classified as inactive with the use of the leaving groups known so far, e.g. SNAC, see page 16, lines 6-9.

Hence, no conclusions as to the predictability or unpredictability of the present invention can be drawn from (failing) experiments with SNAC substrates. Indeed, the success rate of experiments with the presently claimed leaving groups is considerably higher compared to the state of the art, cf. page 16, line 9 of the specification. Insofar,

predictability of the art regarding the claimed subject matter is given or at least greatly enhanced.

For the sake of completeness, it is submitted that the predictability of the art has to be considered in the context of all *Wands* factors. As clearly stated in the Manual of Patent Examining Procedure (MPEP) 2164.01(a), it would be improper to conclude that a disclosure is not enabling based on an analysis of only one of the factors while ignoring one or more of the others. Above, it has been demonstrated that

(1) the quantity of experimentation necessary is little in light of the high success rate of the compounds of the invention, cf. page 16, lines 6-19;

(2) the amount of guidance and working examples presented in the application is ample, cf. e.g. pages 28-33; and

(3) the breadth of the claims is adequate in light of the narrow definition of the leaving groups being charge-stabilized, i.e., being chemical compounds which possess a thio or hydroxyl group and in which the free electron pair of the thiolate or hydroxylate ion stands in conjugation with other electron pairs.

Under consideration of these additional factors and the arguments presented above it is submitted that the present invention is sufficiently enabled over the entire scope of the claims. The Examiner is therefore respectfully requested to withdraw the rejection under 35 USC § 112.

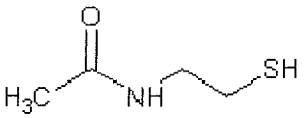
Claim Rejections – 35 USC § 102 and 103

Rejection based on Walsh

Claims 1, 3, 4, 15, and 16 stand rejected under 35 U.S.C. 102(b) as being anticipated by United States Patent Application No. 2002/0192773 to Walsh. Walsh describes the preparation of macrocyclic molecules from linear, synthetic thioester precursors. The cyclization reaction is catalyzed by an excised thioesterase domain isolated from either a PKS or NRPS multidomain system. In this context, a substrate leaving group SR is employed which can be N-acetylcysteamine, i.e., SNAC.

However, in contrast to the Examiner's allegation, SNAC as well as the other substrate leaving groups SR mentioned in Walsh are all but charge-stabilized.

SNAC has the following chemical formula:



When cleaving off this leaving group, there is no charge stabilization in the leaving group whatsoever. Neither a conjugation with an aromatic or heteroaromatic system nor stabilization by the inductive effect of an aromatic system is available, see page 4 lines 29-33 of the specification. The same applies to all other leaving groups SR disclosed by Walsh, particularly when R is a lower alkyl as defined, for example, in paragraphs [0025], [0036], and [0040]. Hence, Walsh cannot anticipate the feature that the leaving group is "charge-stabilized".

This is even more the case as the charge-stabilized leaving groups according to the present invention are narrowly defined as chemical compounds which possess a thio or hydroxyl group and in which the free electron pair of the thiolate or hydroxylate ion released by the acylation reaction stands in conjugation with other electron pairs (page

11, lines 25-33). As a consequence, present claim 1 is novel over Walsh. Since objected claims 3, 4, 15, and 16 are dependent on and/or refer back to claim 1, they also contain the feature that the leaving group is "charge-stabilized". Hence, these claims are also novel over Walsh for the above reasons.

Further, although not objected by the Examiner, it is pointed out that the present set of claims is also non-obvious over Walsh. Walsh does not give any hint or suggestion to use a charge-stabilized nucleophilic leaving group in the context of the disclosed cyclization reaction. Hence, there was room for improvement not only in terms of the yield of known cyclic peptides but also in the ability to obtain cyclic compounds which did, so far, not show any cyclization activity with the respective enzyme on using the known leaving groups (such as fengycin, mycosubtilin, syringomycin and bacitracin; see page 3, lines 13-17 of the specification. Therefore, inventive activity was necessary to arrive at the subject matter of the present set of claims.

Rejections based on Grunewald and Sieber

Regarding the rejections under 35 U.S.C. 102(a) and 35 U.S.C. 103(a) based on Grunewald (Biochemistry. 2004. 43: 2915-2925) and Sieber (Angew. Chem. 2004. 43: 493-498) the Examiner's attention is drawn to the fact that these references were published after the priority date of the present application. Whereas the present application validly claims the priority of DE 103 35 584 which was filed on July 31, 2003, Grunewald was published on February 20, 2004 and Sieber was published on January 14, 2004.

To perfect the filing date of the priority application, Applicants will submit a verified English translation of the priority application that demonstrates that Applicants are entitled to the July 2003 filing date. Hence, the rejections raised on pages 8 (second paragraph) to 12 (first paragraph) of the Office Action will be moot as being based on publications that are not prior art against the claims.

Applicants expect to provide the translation before the Examiner has to work on this application. However, if the Examiner reviews this amendment prior to the filing of the translation, the Examiner is requested to telephone the undersigned if the translation is the only issue preventing allowance of the application.

Restriction Requirement

In response to the Examiner's criticism of claim 10 and its failure to share the common technical feature of claim 1, claim 10 is revised, essentially incorporating the feature of claim 11 therein, which parallels the language found in claim 1 that the acyl group of the C-terminal amino acid of the linear peptide is bound to one of the charge leaving groups. With this change, claims 1 and 10 share the same common technical feature and the restriction requirement requiring the withdrawal of claim 10 and its dependent claims should be withdrawn.

Further, the above conclusions regarding novelty and inventive step of claim 1 equally apply to dependent claims 6-9, which were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as allegedly pertaining to a nonelected invention. It has been shown that the use of a charge-stabilized leaving group is novel and inventive over the prior art. Hence, this feature can be regarded the single common technical

feature of the invention. Due to the fact that claims 6-9 are dependent on claim 1, they all incorporate said feature and thus belong to the elected invention. The Examiner is therefore kindly requested to rejoin claims 6-9 and also acknowledge their allowability.

The same reasoning applies to method claims 10-14 and these claims should be rejoined and allowed with the other claims pending in this application.

Summary

As a result of this filing, each of the issues raised in the Office Action has been addressed so that the application satisfies 35 USC §101/102/103/and 112.

Accordingly, the Examiner is requested to examine this application and pass all pending claims onto issuance.

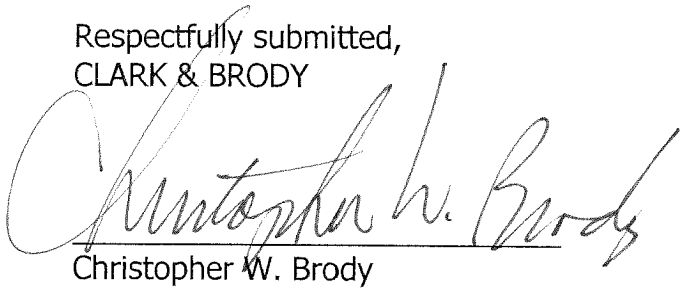
If the Examiner believes that an interview would be helpful in expediting the allowance of this application, the Examiner is requested to telephone the undersigned at 202-835-1753.

The above constitutes a complete response to all issues raised in the outstanding Office Action.

Applicants petition for a two month extension of time. The extension of time fee is paid in connection with the electronic filing of this amendment.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 50-1088.

Respectfully submitted,
CLARK & BRODY



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